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NONSMOKER LUNG CANCER RISKS FROM TOBACCO SMOKE EXPOSURE: AN EVALUATION OF REPACE AND LOWREY'S PHENOMENOLOGICAL MODEL

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INTRODUCTION

Nonsmokers may be exposed to measurable amounts of tobacco smoke in indoor environments such as offices; public areas such as shopping centers, bars and restaurants; and private residences, particularly if the ventilation is poor. This passive exposure to environmental tobacco smoke (ETS) is of concern because several epidemiological studies have indicated that ETS exposure may increase the risk of lung cancer (1,2). The magnitude of a possible excess lung cancer risk for nonsmokers from ETS exposure is therefore of interest.

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Repace and Lowrey (3) develop a "phenomenological model" which estimates an annual excess risk from ETS exposure of 7.4 lung cancer deaths (LCD)/100,000 nonsmokers 35 years of age and over. The risk calculation is limited to individuals 35 years of age and over because only 0.26% of lung cancer deaths in 1980 occurred among individuals less than 35 years of age (4). This excess risk, applied to an estimated U.S. population of 62.4 million nonsmokers, 35 years of age and over, predicts 4,655 nonsmoker lung cancer deaths from ETS exposure. The category "nonsmoker" includes both ex-smokers and life-long never smokers.

Repace and Lowrey's phenomenological estimate of the lung cancer risk from ETS exposure has been widely accepted in the U.S. and Canada (5). Yet, the estimate is based on several unrealistic assumptions and on unstable data that warrant closer examination. It is the purpose of this review to examine several problems with the phenomenological model and to evaluate the reliability of the lung cancer risk estimates derived from it.

THE PHENOMENOLOGICAL MODEL

Repace and Lowrey's phenomenological model extrapolates from the observed (hence phenomenological) results of a study on a special group of never smokers to the entire U.S. population of nonsmokers. The calculations use lung cancer incidence data from a cohort study by Phillips et al (6,7) of California Seventh Day Adventist (SDA) never smokers and a second cohort of California never smokers. The SDA cohort of never smokers were followed prospectively from 1960 until mid-1972 and the comparison never smoker cohort, from the American Cancer Society (ACS) 25-state study, was followed from 1960 to the end of 1976.

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The study by Phillips et al does not examine the association between ETS exposure and lung cancer, nor is any information obtained on ETS exposure. However, the SDA group was probably less exposed to ETS than the nonSDA group because less than two percent of the SDAs were self-reported smokers as a result of the church proscription against smoking. Consequently, SDA never smokers are not likely to be exposed to ETS in church operated businesses, in their own homes, or in the homes of other church members.

Table I gives, for both SDA and nonSDA never smokers, the observed number of lung cancer deaths and the lung cancer death rate per 100,000 person-years for each 5-year age group starting from age 35. The age standardized relative risk of lung cancer for the SDA men and women compared to the nonSDA men and women is 1.73 and 2.54, respectively.

Repace and Lowrey assume that *all* of the difference in the lung cancer risk between SDA and nonSDA never smokers is caused by a difference in exposure to ETS. They estimate the lung cancer risk from ETS exposure in the following manner. First, the age-specific lung cancer risks for SDA never smokers are subtracted from the comparable risks for nonSDA never smokers. For example, the lung cancer death rate for nonSDA never smoking women 85 years of age and over is 126.73 per 100,000 (Table I, column 5), while the rate for the comparable group of SDA women is 22.54 (Table I, column 3). The difference, 104.19 LCD/100,000, is attributed entirely to ETS exposure. Second, the age-specific differences in risk for men and women are weighted in order to derive a single age-specific risk estimate. For example, the difference between SDA and nonSDA men over 85 is 48.96 LCD/100,000. The combined average for the over 85 age group, weighted by the number of person-years of observation for

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TABLE I

Number of lung cancer deaths and the lung cancer death rate per 100,000 person-years (LCD/100,000) for Seventh Day Adventist (SDA) and nonSDA never smokers (1)

MEN	SDA		nonSDA	
Age	# Deaths*	LCD/100,000	# Deaths*	LCD/100,000
35-39	0	0	0	0
40-44	0	0	0	0
45-49	0	0	0	0
50-54	0	0	1	5.18
55-59	1	10.80	2	8.39
60-64	1	11.44	4	20.48
65-69	4	46.04	8	56.72
70-74	1	17.53	0	0
75-79	0	0	2	30.58
80-84	1	28.89	4	113.73
85+	2	70.73	2	119.69

WOMEN	SDA		nonSDA	
Age	# Deaths*	LCD/100,000	# Deaths*	LCD/100,000
35-39	0	0	0	0
40-44	0	0	1	6.07
45-49	0	0	2	5.22
50-54	1	4.51	4	6.49
55-59	1	4.05	8	11.22
60-64	1	4.58	7	10.76
65-69	1	4.92	4	7.19
70-74	0	0	9	20.34
75-79	1	5.32	10	34.19
80-84	8	57.87	6	39.21
85+	2	22.54	10	126.73

*The actual number of observed deaths is estimated from Repace and Lowrey's figures, which were adjusted for the effect of outmigration.

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men and women, is 92.6 LCD/100,000. Third, the average risk estimates for both sexes combined are applied to the estimated population distribution of the 62.4 million nonsmokers 35 years of age and over in the U.S. in 1980, which is assumed to be the same as the age distribution of the entire U.S. population in 1974. For example, the excess lung cancer risk from ETS exposure of 92.6 LCD/100,000 men and women 85 years of age and over, combined, is applied to the estimated 981,164 nonsmokers over 85 in the U.S. in 1980. This predicts 909 excess lung cancer deaths in this age group [(92.6 x 981,164)/100,000]. Fourth, the excess lung cancer deaths for all age groups over 35 are summed. This adds up to 4,655 excess lung cancer deaths among the 62.4 million nonsmokers, which gives an annual risk from ETS exposure of 7.4 LCD/100,000 nonsmokers 35 years of age and over.

PROBLEMS WITH THE PHENOMENOLOGICAL MODEL

There are three problems with Repace and Lowrey's phenomenological model.

1. The lung cancer risk estimates derived from the SDA study are based on very few observed deaths and are unstable.
2. The apparent differences in lung cancer mortality between SDA and nonSDA never smokers may be due to a variety of factors other than ETS exposure.
3. A number of assumptions and calculations are made that are clearly incorrect.

1. Stability of the Model

The reliability of Repace and Lowrey's phenomenological model is strongly dependent upon the accuracy of the

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age-specific lung cancer death rates calculated for the SDA and nonSDA never smokers. However, the SDA lung cancer death rates, in particular, are not likely to be accurate because they are based on a small number of observed lung cancer deaths.

There were only 10 lung cancer deaths among the SDA men (the difference in risk between SDA and nonSDA men is not, in fact, statistically significant) and 15 deaths among the SDA women (6). The age-specific risks for 9 out of the 22 age groups are based on only one lung cancer death and there were no lung cancer deaths in an additional nine of the age groups. Consequently, the age-specific rates for SDA men and women varied widely, as shown in column 3 of Table I. For example, the lung cancer death rate for SDA women over 85 was less than half the rate for the preceding age group. This decline of lung cancer risk with age must be due to random or other errors, because lung cancer death rates invariably increase with age (8,9).

The small number of lung cancer deaths observed for the SDA cohort may be partly attributable to a lack of histopathological verification and incomplete follow-up. These two problems did not occur in the nonSDA cohort, which may partly explain the large difference in the lung cancer rates between the two cohorts. The SDA cohort was also relatively small so that few lung cancer deaths would be expected. Random fluctuations in the number of observed lung cancer deaths would result in large differences in the age-specific lung cancer death rates. Therefore, these rates are very unstable.

The phenomenological model is very sensitive to errors in the estimated lung cancer death rates for SDA never smokers. For example, adding one lung cancer death to the 70-74 year age

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group for SDA women results in 183 fewer estimated deaths per year in the U.S., according to the method used by Repace and Lowrey (3). A second example concerns the over 85 age group. As noted above, the observed lung cancer death rate of 22.5 LCD/100,000 SDA women 85 years of age and older is not likely to be correct, and is probably a large underestimate of the true rate. This underestimate is responsible for a significant proportion of all lung cancer deaths attributed to ETS exposure. 909, or 19.5%, of the estimated 4,655 excess lung cancer deaths in the U.S. among all nonsmokers 35 years of age and over occur among individuals over 85 years of age. The majority of these deaths are attributable to the estimated risk for women over 85 because of the large difference of 104.2 LCD/100,000 between the rate of 22.5 LCD/100,000 SDA women and 126.7 LCD/100,000 nonSDA women in this age group. An increase in the lung cancer death rate for SDA women over 85 years of age to a rate greater than that observed for women between 80-84 years of age (57.9 LCD/100,000) would decrease the difference between the SDA and nonSDA cohorts and consequently decrease the predicted risk and number of deaths attributable to ETS exposure.

For several age groups, the phenomenological model predicts more lung cancer deaths among never smokers as a result of exposure to ETS alone than a reasonable estimate of the total number of lung cancer deaths from all causes, as shown in Table II for men and Table III for women. The number of expected lung cancer deaths is obtained by multiplying the age-specific lung cancer death rates from ETS exposure alone (column 3) or from all causes (column 5) by an estimate of the number of never smokers in each age and sex category (column 2). The latter is obtained by combining the 1979/1980 Health Interview Survey

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TABLE II

Comparison of the estimated number of lung cancer deaths (LCD) in 1980 among male never smokers from exposure to environmental tobacco smoke (ETS) and from all causes

		ETS EXPOSURE		ALL CAUSES	
Age	Never-smoking Population*	LCD/100,000**	Estimated Deaths†	LCD/100,000††	Estimated Deaths†
35-39	1,993,771	0	0	0	0
40-44	1,713,901	0	0	7.6667	131.3896
45-49	1,239,080	0	0	3.0333	37.5690
50-54	1,328,782	5.1779	68.80		
55-59	1,127,890	-2.4152	-27.24	10.1333	114.2884
60-64	1,162,938	9.0651	105.38	17.2667	200.7314
65-69	1,084,361	10.6740	116.81	27.4333	300.2193
70-74	886,253	-17.9301	-159.38	77.9000	690.3811
75-79	722,398	30.5764	220.88	44.2667	319.7818
80-84	382,727	84.8475	324.73	68.6667	263.5715
85+	303,790	48.9412	148.74	94.8000	287.9928
			Total 802.74		Total 2,447.38

* Estimated from the 1979/1980 HIS distribution of never smokers of all races and the U.S. Census (10) estimate of the population size in 1980.
** From Table C1, column 9, Repace and Lowrey (3). Each age-specific rate is the LCD/100,000 nonSDA never smokers per year minus the rate for the SDA never smokers.
†Equals the relevant LCD/100,000 times the never smoking population divided by 100,000.
†† Average lung cancer death rates per year for 1960-1972 for the ACS population of never smokers (8).

TABLE III

Comparison of the estimated number of lung cancer deaths (LCD) among female never smokers from exposure to environmental tobacco smoke (ETS) and from all causes

		ETS EXPOSURE		ALL CAUSES	
Age	Never-smoking Population*	LCD/100,000**	Estimated Deaths†	LCD/100,000††	Estimated Deaths†
35-39	3,388,446	0	0	0	0
40-44	2,870,212	6.0731	174.31	2.3333	66.97
45-49	2,887,920	5.2193	150.71	3.6000	103.96
50-54	3,243,330	1.9903	64.21	5.3000	171.84
55-59	3,147,137	7.1737	225.77	7.0667	222.40
60-64	2,982,713	6.1623	184.40	13.6000	405.65
65-69	2,979,828	2.2710	67.67	16.1667	481.74
70-74	2,616,364	20.3400	532.17	20.8333	545.06
75-79	2,157,707	28.8750	623.04	34.7000	748.72
80-84	1,528,857	-16.6560	-265.22	43.8000	700.22
85+	1,026,930	104.1890	1,066.93	92.4667	936.80
			Total 2807.01		Total 3,985.37

* Estimated from the 1979/1980 HIS distribution of never smokers of all races and the U.S. Census (10) estimate of the population size in 1980.
** From Table C1, column 9, Repace and Lowrey (3). Each age-specific rate is the LCD/100,000 nonSDA never smokers per year minus the rate for the SDA never smokers.
†Equals the relevant LCD/100,000 times the never smoking population divided by 100,000.
†† Average lung cancer death rates per year for 1960-1972 for the ACS population of never smokers (8).

(HIS) estimates of the proportion and age and sex distribution of never smokers with the U.S. Census estimate of the population 35 years of age and over in 1980 (10,11). The estimated number of lung cancer deaths from ETS exposure alone is given in column 4 of each table. The all causes estimate uses the lung cancer death rates observed for never smokers in the ACS 25-state study (8). The estimated number of lung cancer deaths from all causes is given in column 6 of each table.

The phenomenological model estimates fewer male never smoker lung cancer deaths from ETS exposure than the estimated number of deaths from all causes. However, for women, the model estimates almost the same number of lung cancer deaths from ETS exposure than from all causes for the age group 70-74 and more deaths from ETS exposure than from all causes for the age groups 40-44, 45-49, 55-59 and 85+. For example, the estimate of 1,069 female deaths attributable to ETS exposure in the 85+ group is almost twice the estimate of 539 deaths from all causes. The fact that the phenomenological model predicts, for several age groups, more lung cancer deaths from ETS exposure alone than from all causes indicates that the death rates used in the model are unreliable indicators of the real risk associated with ETS exposure.

2. Other Causes for the Difference in Risk Between SDA and NonSDA Nonsmokers

Repace and Lowrey's phenomenological model assumes that all of the difference in lung cancer incidence between the SDA and nonSDA never smokers is caused by ETS exposure. This assumption does not allow for other possible confounding factors, such as

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differences between the SDA and nonSDA cohorts in diet or exposure to occupational carcinogens.

The possibility of confounding by occupation, though possible, cannot be assessed. Phillips et al (6,7) did not determine the occupational distribution of SDA and nonSDA never smokers because occupation was coded differently for the two groups. Occupation would affect the estimated risks if a higher proportion of the nonSDA versus SDA never smokers were blue-collar workers exposed to carcinogens at work.

Confounding by diet is probable. A low rate of consumption of vegetables or foods containing retinoids has been linked to an increased lung cancer risk (12-15). The SDAs are known to follow a lacto-ovo vegetarian diet and this may reduce their risk for many types of cancer, both through a decreased intake of fats and an increased consumption of vegetables, eggs, and milk high in retinoids or vitamin A. Therefore, the low lung cancer incidence among the SDA never smokers may be due to dietary factors such as an above average consumption of retinoids. A possible dietary cause for the difference in the lung cancer risk between the SDA and nonSDA never smokers is supported by the lower risks for colon-rectal and breast cancer observed for the SDA group. Several studies have found that diet may be a risk factor for colon-rectal (16) and breast cancer (17). There was a statistically significant decrease in the relative risk (RR) of breast cancer (RR = 0.81) and colon-rectal cancer (RR = 0.56) for SDA women never smokers compared to the nonSDA women never smokers (6). The relative risk of colon-rectal cancer for SDA men was also below 1.0 but was not statistically significant.

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3. Other Errors

There are three instances where Repace and Lowrey make inappropriate assumptions.

1. Repace and Lowrey incorrectly assume that nonsmokers have the same sex and age distribution as the entire U.S. white population. A comparison between the 1979/1980 HIS data and U.S. Census data (10) shows that the age distribution of the U.S. nonsmoking population is skewed towards the older age classes, as shown in Table IV. For example, 25.38% of male nonsmokers 35 years of age and over are between the ages of 35 and 44 compared to 28.76% of all U.S. males 35 years of age and over and 10.5% of nonsmoking males are 75 years of age or over compared to 8.1% of all U.S. males.
2. Repace and Lowrey combine both sexes, instead of calculating the expected number of deaths for each sex separately. The latter is required, as the age distribution of female never and nonsmokers is different from the comparable distributions for men, as shown in Table IV.
3. Repace and Lowrey estimate the excess lung cancer deaths from ETS exposure for nonsmokers (ex- and never smokers combined). This should not be done because the difference in lung cancer death rates between the SDA and nonSDA group is for *never* smokers only. The excess risk for ex-smokers from exposure to ETS may differ from the risk for never smokers, either because of their previous smoking habit or because ever smokers are more likely than never smokers to be exposed to carcinogens at work (18).

IS THERE INDEPENDENT SUPPORT FOR THE PHENOMENOLOGICAL MODEL?

The phenomenological model, based on only 25 lung cancer deaths among never smoking men and women SDAs combined, provides

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TABLE IV

1979/1980 HIS estimates of the age distributions of never and nonsmokers and the U.S. Census estimate for adults 35 years of age and over

MEN

	HIS		U.S. Census
Age	Never	Nonsmoker	All
35-44	31.00	25.38	28.76
45-54	21.47	23.01	24.80
55-64	19.15	22.40	23.00
65-74	16.56	18.66	15.34
75-84	9.24	8.44	6.54
85+	2.54	2.06	1.56

WOMEN

	HIS		U.S. Census
Age	Never	Nonsmoker	All
35-44	21.70	23.09	25.38
45-54	21.25	21.67	22.67
55-64	21.25	21.92	22.34
65-74	19.40	19.21	17.10
75-84	12.78	11.14	9.46
85+	3.56	2.82	3.05

an unstable estimate of the lung cancer risk for nonsmokers as a result of ETS exposure. Repace and Lowrey, though not directly addressing this problem, use corroborative evidence to defend the estimated annual risk of 7.4 LCD/100,000. They argue that their findings are supported by 1) the results of a linear extrapolation model, after adjusting for the nonsmoker's retained ETS dose and 2) a sensitivity analysis of the ACS study on ETS exposure and lung cancer (8).

1. Linear Extrapolation Model

Nonsmoker lung cancer risks from ETS exposure can be calculated by using a linear extrapolation model. This method

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estimates the risk for nonsmokers by dividing the lung cancer risk for current smokers by the ratio between the smoker's and nonsmoker's average exposure. The linear model requires estimates of several parameters such as the number of nonsmokers and current smokers in the U.S. and their average daily exposure to ETS. The linear extrapolation model also requires three assumptions, 1) that it is valid to derive the lung cancer risk for nonsmokers exposed to ambient ETS from the observed risk for smokers exposed to directly inhaled tobacco smoke, 2) that there is a linear relationship between risk and each unit of exposure, and 3) that no threshold exists at very low exposures where the risk falls to zero.

Repace and Lowrey (3) pioneered the development of the linear model for estimating nonsmoker lung cancer risks from ETS exposure. Their linear extrapolation calculation estimates a lung cancer risk for nonsmokers of 0.83 LCD/100,000 from ETS exposure. This is significantly lower than the phenomenological model's estimate of 7.4 LCD/100,000. Repace and Lowrey argue that the difference between the two risk estimates can be explained by the difference between the nonsmoker's inhaled exposure and the equilibrium ETS dose.

The inhaled exposure is based on the amount of ETS inhaled, whereas the equilibrium dose calculates the steady-state burden of particulate ETS in the lungs from the inhaled exposure. The following equation calculates the equilibrium dose (3):

$$\text{Equilibrium dose} = Dn\delta\tau,$$

where Dn equals the inhaled exposure in milligrams (mg); δ equals the deposition fraction for tobacco smoke particulates in the lungs; and τ equals the mean life for pulmonary clearance,

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which is assumed to be 101 days. The deposition fraction for nonsmokers has been empirically estimated to be approximately 11% (19). Repace and Lowrey estimate that the equilibrium dose for the average nonsmoker inhaling 1.43 mg/day is 16 mg/day (1.43 mg x .11 x 101), which is 1/34th of their estimate of the average smoker's daily inhaled exposure of 544 mg. Repace and Lowrey's estimate of the lung cancer risk for current smokers is 315.6 LCD/100,000. Therefore, the linear model predicts a lung cancer risk for never smokers of 9.28 LCD/100,000 (315.6/34). Accordingly, the risk estimates derived from the linear and phenomenological models are approximately the same, with the phenomenological model providing the lower risk estimate.

In fact, Repace and Lowrey's adjustment of the linear model is based on an incorrect comparison between two completely different estimates of exposure. The *exposure* of smokers is compared to the *equilibrium dose* of nonsmokers. Obviously, the correct comparison is either between the smoker and nonsmoker's inhaled exposure or between the smoker and nonsmoker's equilibrium dose. An estimate of the lung cancer risk for nonsmokers, using the linear model and the equilibrium dose, can be determined using an estimate of the deposition fraction for smokers.

The deposition fraction for smokers has been empirically estimated to be between 70% and 96% (19-22). We will assume an average retention rate of 80% for smokers. The equilibrium dose for smokers, using Repace and Lowrey's estimate of the inhaled exposure for smokers of 544 mg, is 43,955 mg (544 x 0.80 x 101). Therefore, nonsmokers have only 1/2,747th of the smoker's equilibrium dose (43,955/16) and, consequently, only 1/2,747th of the smoker's lung cancer rate, or 0.11 LCD/100,000

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(315.6/2,747). Instead of supporting the phenomenological estimate, the use of the equilibrium dose in the linear model significantly decreases the likelihood that the phenomenological model provides a reliable estimate of the average risk for nonsmokers from ETS exposure.

2. Sensitivity Analysis

Repace and Lowrey (3) conduct a sensitivity analysis to explain the difference in the results of two cohort studies, one in Japan and one in the U.S., of female nonsmokers married to smokers. The sensitivity analysis uses an estimate of risk per 1 mg of exposure to tobacco smoke particulate that is based on the phenomenological model. Garfinkel's (8) analysis of the ACS data for 176,731 American women followed from 1960 until 1971 finds a statistically nonsignificant increased relative risk of 1.20 for never smoking women married to smokers. Conversely, Hirayama's (23) study of 91,540 Japanese women followed from 1966 to 1981 finds a statistically significant increased relative risk of 1.78, which is closer to the relative risk of 1.73 for men and 2.54 for women on which the phenomenological model is based.

Repace and Lowrey suggest that the ACS relative risk is unrealistically low and actually results from confounding with workplace exposure, which they estimate to contribute four times as much exposure to ETS as the home environment. The ACS study does not include workplace exposure as a factor in deciding exposure status. Nonsmoking women married to smokers are defined as exposed, whereas nonsmoking women married to nonsmokers are defined as unexposed. Repace and Lowrey estimate that 38 percent

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of the original unexposed and exposed ACS women worked outside the home and were therefore exposed to ETS at work.

Repace and Lowrey's sensitivity analysis recalculates the ACS results using an estimate of the lung cancer risk per 1 mg of ETS exposure and an estimate of the amount of home and workplace exposure recieved by the original ACS exposed and unexposed cohorts. The lung cancer risk per 1 mg of exposure is estimated by combining the phenomenological model's estimated risk of 7.4 LCD/100,000 with an estimated average daily exposure to 1.43 mg of ETS. This estimates a risk of 5 LCD/100,000 per mg of exposure. The excess lung cancer risk from ETS exposure for each of four exposure categories - women not exposed at home or at work, women exposed at work only, women exposed at home only, and women exposed at home and at work - is determined by multiplying the estimated exposure by the risk of 5 LCD/100,000 per mg of exposure. For example, Repace and Lowrey estimate that employed women are exposed to 1.82 mg/day and women who live with a smoker are exposed to 0.45 mg/day. Therefore, women who both work and live with a smoker are exposed to 2.27 mg/day for an excess risk of 11.35 LCD/100,000 (2.27 x 5). The excess risk from ETS exposure is added to the background lung cancer risk in the absence of any exposure in order to construct an expected death rate for each of the four exposure categories. The lung cancer death rate of 8.7 per 100,000 person-years found in the Japanese cohort study for nonsmoking women married to nonsmoking men is used as the base lung cancer rate in the absence of either work or home exposure to ETS.

The relative risk of 1.19 for women who live with a smoker versus those who do not, determined after the adjustment for work exposure and the use of the phenomenological model's

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estimate of risk, is only marginally different from the original "unadjusted" risk of 1.20. According to Repace and Lowrey, this indicates that the estimated risk from the phenomenological model is a good estimator of the true risk in this cohort study.

Problems with the sensitivity analysis

Repace and Lowrey's sensitivity analysis is dependent upon 1) the applicability of the background lung cancer death rate in the absence of smoking and 2) the relative importance of exposure at work versus exposure at home.

1. The background risk

The use of the risk of 8.7 LCD/100,000 Japanese women nonsmokers as an estimate of the background risk in the Garfinkel study is inappropriate. Repace and Lowrey note that the risk of 8.7/100,000 is an 'age-adjusted' risk, *but it is adjusted to the age distribution of the husbands of the Japanese female nonsmokers and not to the ACS women at risk.* It is unlikely that the age distribution of Japanese male nonsmokers is the same as the age distribution of American female nonsmokers.

The age distribution of the entire ACS population of nonsmoking women is available and can be compared against the age distribution used in Hirayama's study. Both distributions are given in Table V. If we assume that the age distribution of nonsmoking women married to nonsmokers in the ACS study is similar to the age distribution of all nonsmoking ACS women, it is possible to apply the age-specific lung cancer death rates from the Japanese study to the ACS population distribution, as shown in Table VI. The background lung cancer death rate is

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TABLE V

Age distribution of 375,381 nonsmoking women at the start of the ACS study and the nonsmoking husbands of 21,895 nonsmoking women at the start of the Hirayama study

AGE	ACS (24)	Hirayama (1)
under 49*	0.3374	0.2845
50-59	0.3278	0.3558
60-69	0.2201	0.3252
70+	0.1147	0.0345

* ACS population starts at 30 years of age and the Hirayama population of husbands at 40 years of age.

TABLE VI

Estimated lung cancer death rate (LCD/100,000) for nonsmoking women from the ACS study (8) after using the husband-age-specific risks for nonsmoking women from Hirayama (1)

AGE	Hirayama: LCD/100,000*	Age Distribution of ACS nonsmokers	Expected LCD's
under 49	4.01	0.3374	1.35
50-59	8.02	0.3278	2.63
60-69	15.80	0.2201	3.48
70+	41.39	0.1147	4.75
		Total LCD/100,000	12.21

* Age-specific LCD/100,000 person years, adjusted for the husband's age (1).

subsequently increased from 8.7 to 12.21 LCD/100,000. This is similar to the rate for all nonsmoking ACS women of approximately 13/100,000, which indicates that there is no increase in risk in the ACS study from ETS exposure.

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The background risk of 12.21 LCD/100,000 can be used in the sensitivity model, keeping in mind that the model is extremely insensitive to large differences in risk. For example, the use of the phenomenological estimate of the excess lung cancer risk from ETS exposure results in a 1% difference between the adjusted relative risk of 1.19 and the observed relative risk of 1.20. Decreasing the estimate of the excess risk 8.3-fold only increases the difference between the adjusted and observed relative risks by 17%. A change in the background risk from 8.7 LCD/100,000 to 12.21 LCD/100,000 increases the difference between the adjusted and observed relative risk from 1.0% to 4.6%, which is a significant change considering the insensitivity of the sensitivity analysis. This indicates that the estimate of risk from the phenomenological model is a poor indicator of the true risk in the ACS population.

The use of the background lung cancer rate from the Japanese study is also questionable. It assumes that none of the Japanese women worked. Accordingly, it is unnecessary to adjust their baseline lung cancer death rate for workplace exposure to ETS. In fact, between 31% and 34% of Japanese women worked in paid employment during the time period of the Hirayama study (25), and 15% of Japanese women smoked (26). Therefore, some workplace exposure must have occurred from exposure to the tobacco smoke of fellow male and female employees.

2 Adjustment for work exposure

The sensitivity analysis is dependent upon Repace and Lowrey's estimate, based on an exposure model, that workplace exposure accounts for 80.4% of the total daily average exposure to ETS, while home exposure accounts for only 19.6%. However, there is no independent supporting evidence for Repace and

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Lowrey's estimate on the relative importance of workplace versus home exposure from interview data (27) or from epidemiological studies. None of the four epidemiological studies which specifically examine the effect of exposure of women to ETS at work finds a statistically significant increase in risk (15,28-30).

DISCUSSION AND CONCLUSIONS

Other than Repace and Lowrey's phenomenological model, two methods are available for estimating the lung cancer risk or number of lung cancer deaths among nonsmokers from ETS exposure. These methods consist of 1) a downward extrapolation from the risk for smokers and 2) the population attributable risk (PAR) equation (31).

The linear extrapolation model was developed by Repace and Lowrey (3) and has been further refined by Arundel et al (32). As shown above, Repace and Lowrey's linear model does not support the results of the phenomenological model. In addition, the risk estimate of 0.83 LCD/100,000 nonsmokers, determined by Repace and Lowrey from the linear model, is inaccurate. This is because their linear model overestimates the average nonsmoker's exposure to ETS and the average current smoker's lung cancer risk. For example, the latter is estimated by Repace and Lowrey after assuming that all lung cancer deaths among ever smokers (ex- and current combined) occur only among current smokers. This results in a significant overestimate of the lung cancer risk for current smokers and, subsequently, for never smokers.

The linear model developed by Arundel et al (32) estimates a lung cancer risk from ETS exposure for both sexes combined of 0.022 LCD/100,000. This estimate is based on the equilibrium

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dose. However, the calculations by Arundel et al, as do those by Repace and Lowrey, rest on several assumptions that may not be tenable.

The large difference in the linear estimates by Repace and Lowrey and by Arundel et al illustrates the extensive uncertainty which accompanies the results of these types of models. Large errors in the risk estimates are possible in any type of model. Arundel et al provide a "sensitivity calculation" which indicates the effect of a 1% change in each parameter of the linear model on the final risk estimate. This is useful for determining the most important parameters in the model, but does not replace scientifically desirable confidence limits.

The PAR equation estimates the number of lung cancer deaths from ETS exposure using differences in risk observed in epidemiological studies. In this respect it is similar to the phenomenological model, but the number of lung cancer deaths from ETS exposure is calculated using only three parameters: the exposure rate in the population of interest, the relative risk of exposure, and an estimate of the number of nonsmokers in 1980 (obtainable from the 1979/1980 HIS). Therefore, the PAR equation appears to be a remarkably simple method for estimating the number of lung cancer deaths among nonsmokers from ETS exposure. However, neither the exposure rate nor the relative risk are known for the entire population of nonsmokers. The exposure rate could be estimated from HIS data on the employment status of nonsmokers and the proportion who live with a smoker. Unfortunately, the relative risk cannot be estimated because most of the epidemiological studies on this problem only calculate risks for a subset of all nonsmokers (married women) exposed to a subset of all possible exposures (spouse's smoke) (2,8,23,33-37).

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The relative risk is particularly difficult to obtain because the PAR method requires an estimate of the relative risk for the *average* regularly exposed nonsmoker compared to the *average* unexposed nonsmoker. The relative risk must not be determined from a subset of the regularly exposed population of nonsmokers. Exposure should also be defined as cumulative exposure to all sources of ETS.

An accurate method for estimating the lung cancer risk and the number of lung cancer deaths among nonsmokers from ETS exposure is of considerable interest. Repace and Lowrey's phenomenological estimate of the lung cancer risk for nonsmokers from ETS exposure is unstable and inaccurate. The evidence presented by Repace and Lowrey to support the plausibility of their estimate is based on several errors and unrealistic assumptions. Without corroborating data from independent sources, little confidence can be placed in their results.

The results of the linear extrapolation model by Arundel et al and the results of the best available epidemiological studies further indicate that the phenomenological estimate is in error. Both predict an extremely small excess lung cancer risk from ETS exposure. Conversely, Repace and Lowrey argue that the 12 epidemiological studies on ETS exposure support the plausibility of a significant excess risk from ETS exposure. However, with one exception (for men exposed at work) (29), the observed risks are statistically significant only when the analysis of exposure is limited to a comparison between female never smokers who are currently married to smokers versus married to nonsmokers. Exposure may also occur at work or at home from other household members and from previous spouses. Therefore, epidemiological studies should examine cumulative exposures from all sources.

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The best available epidemiological analyses, by Koo et al (28) in Hong Kong and Garfinkel et al (30) in the United States, examine exposure from all sources. Neither find a statistically significant increase in risk. Garfinkel et al (30) also correlate cumulative exposures from all sources over the previous five or twenty-five years against lung cancer incidence and find a negative correlation between an increase in exposure and lung cancer. These analyses of cumulative exposures indicate that an association between lung cancer among nonsmokers and the spouse's smoking habit may be caused by confounding, not by ETS exposure. Confounding could occur either from life-style factors and occupational exposures associated with active smoking or by unreported active smoking by self-reported nonsmokers (38).

REFERENCES

1. Hirayama, T. Prev. Med. 13:680, 1984.
2. Trichopoulos, D., Kalandidi, A. and Sparros, L. Lancet 2:677, 1983.
3. Repace, J.L. and Lowrey, A.H. Environ. Int. 11:3, 1985.
4. National Center for Health Statistics. United States Dept. of Health and Human Services, Public Health Service. Division of Vital Statistics, Statistical Resources Branch, 1986. Data available on request.
5. Marwick, C. JAMA 24/31:2937, 1985.
6. Phillips, R.L., Ruzma, J.W., Beeson, W.L. and Lotz, T. Am. J. Epidemiol. 112:296, 1980.
7. Phillips, R.L., Garfinkel, L., Ruzma, J.W., Beeson, W.L., Lotz, T. and Brin, B. JNCI 65:1097, 1980.
8. Garfinkel, L. JNCI 66:1061, 1981.
9. Enstrom, J.E. and Godley, P.H. JNCI 65:1175, 1980.

2023381947

10. USDC (United States Dept. of Commerce). Bureau of the Census. Preliminary estimates of the population of the United States, by age, sex, and race: 1970 to 1981. Population Estimates and Projections Series P-25, No. 917, 1982.

11. The HIS is an ongoing survey which uses a probability sample of households in the U.S. The 1979/1980 survey contains smoking, age, and sex information for 37,604 individuals 17 years of age and over. Due to the size of the sample, the HIS provides the best available estimate of the proportion of American adults who are never smokers and their age and sex distributions. A computer readable tape of the 1979/1980 HIS data was obtained from the National Center for Health Statistics. All analyses of the HIS were conducted by us.

12. Wynder, E.L. and Goodman, M.T. Epidemiol. Rev. 5:177, 1983.
13. Byers, T., Vena, J., Mettlin, C., Swanson, M. and Graham, S. Am. J. Epidem. 120:769, 1984.
14. Hinds, M.W., Kolonel, L.N., Hanlan, J.H., and Lee, J. Am. J. Epidemiol. 119:227, 1984.
15. Wu, A.H., Henderson, B.E., Pike, M.C. and Yu, M.C. JNCI 74:747, 1985.
16. Graham, S. in Reviews in Cancer Epidemiology edited by A.M. Lilienfeld. Elsevier. Amsterdam, Oxford. 1983.
17. Miller, A.B., Kelly, A., Choi, N.W., Mathews, V., Morgan, R.W., Munan, L., Burch, J.D., Feather, J., Howe, G.R. and Jain, M. Am. J. Epidemiol. 107:499, 1978.
18. Sterling, T. and Weinkam, J. Arch. Environ. Health 33:313, 1978.
19. Hiller, F.C., McKusker, K.T., Mazumber, M.K., Wilson, J.D. and Bone, R.C. Am. Rev. Respir. Dis. 125:406, 1982.
20. Hoegg, U.R. Environ. Health Perspec. Oct:117, 1972.

Source: https://www.industrydocuments.ucsf.edu/docs/phyx0000

21. Hiller, F.C. Prev. Med. 13:602, 1984.

22. Dalhamn, T. JNCI Mono. 28:79, 1968.

23. Hirayama, T. Br. Med. J. 282:183, 1981.

24. Garfinkel, L. JNCI 65:1169, 1980.

25. JML (Japanese Ministry of Labour). The Status of Wom
Japan Women and Young Workers Bureau, Ministry of L
Tokyo, 1983.

26. Hayashi, T. World Smoking and Health 5:40, 1980.

27. Friedman, G.D., Petitti, D.B. and Baivol, R.D. AJPH
1983.

28. Koo, L.C., Ho, J.H.-C. and Saw, D. J. Exp. Clin. Can.
3:277, 1984.

29. Kabat, G.C. and Wynder, E.L. Cancer 53:1214, 1984.

30. Garfinkel, L., Auerbach, O. and Joubert, L. JNCI 75:46
1985.

31. Cole, P., MacMahon, B. Brit. J. Prev. Med. 25:242, 1971

32. Arundel, A., Irwin, T., Sterling, T. and Wienkam, J.
Submitted for publication. Copy available from the autho
request. 1986.

33. Chan, W.C. and Fung S.C. in Cancer Campaign Vol. 6. Cance
Epidemiology. Gustav Fischer Verlag, Stuttgart.1982.

34. Correa, P., Pickle, L.W., Fontham, E., Lin, Y. and Haensze
W. Lancet 2:595, 1983.

35. Knoth, A., Bohn, H. and Schmidt, F. Med. Klin. 78:66, 1983.

36. Gillis, C.R., Hole, D.J., Hawthorne, V.M. and Boyle, P.
European. J. Respir. Dis. (Suppl.) 133:121, 1984.

37. Sandler, D.P., Everson, R.B. and Wilcox, A.J. Am. J.
Epidemiol. 121:37, 1985.

38. Lehnert, G. Prev. Med. 13:730, 1984.

2023381948

Source: https://www.industrydocuments.ucsf.edu/docs/phyx0000